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(54) **PROCESS FOR THE PREPARATION OF 3-(3-CHLORO-1H-PYRAZOL-1-YL)PYRIDINE**

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(51) **Int. Cl.**
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(52) **U.S. Cl.**
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(57) **ABSTRACT**

3-(3-Chloro-1H-pyrazol-1-yl)pyridine is prepared by cyclizing 3-hydrazinopyridine.dihydrochloride with commercially available 3-ethoxyacrylonitrile to provide 3-(3-amino-1H-pyrazol-1-yl)pyridine, and by converting the amino group to a chloro group by a Sandmeyer reaction.

11 Claims, No Drawings

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PROCESS FOR THE PREPARATION OF 3-(3-CHLORO-1H-PYRAZOL-1-YL)PYRIDINE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 14/517,349 filed on Oct. 17, 2014, which claims the benefit of U.S. Provisional Patent Application Ser. No. 62/031,533, filed Jul. 31, 2014, the entire disclosures of which are hereby expressly incorporated by reference in this Application.

BACKGROUND

The present invention concerns an improved process for preparing 3-(3-chloro-1H-pyrazol-1-yl)pyridine.

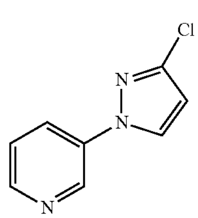
US 20130288893(A1) describes, inter alia, certain (3-halo-1-(pyridin-3-yl)-1H-pyrazol-4-yl)amides and carbamates and their use as pesticides. The route to prepare such compounds involved the preparation of 3-(3-chloro-1H-pyrazol-1-yl)pyridine (5b) by the direct coupling of 3-bromopyridine with 3-chloropyrazole. The 3-chloropyrazole was prepared by a) treating 1H-pyrazole with 2-dimethylsulfamoyl chloride and sodium hydride to provide N,N-dimethyl-1H-pyrazole-1-sulfonamide, b) treating the N,N-dimethyl-1H-pyrazole-1-sulfonamide with perchloroethane and n-butyl lithium to provide 3-chloro-N,N-dimethyl-1H-pyrazole-1-sulfonamide, and c) removing the N,N-dimethylsulfonamide from 3-chloro-N,N-dimethyl-1H-pyrazole-1-sulfonamide with trifluoroacetic acid to give the 3-chloropyrazole.

The disclosed process produces low yields, relies on a starting material that is difficult to prepare (3-chloropyrazole) and provides a product that is difficult to isolate in a pure form. It would be desirable to have a process for preparing 3-(3-chloro-1H-pyrazol-1-yl)pyridine that avoids these problems.

SUMMARY

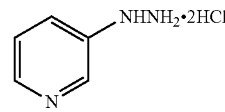
The present invention provides such an alternative by cyclizing 3-hydrazinopyridine.dihydrochloride with commercially available 3-ethoxyacrylonitrile to provide 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a), and by converting the amino group to a chloro group by a Sandmeyer reaction. Thus, the present invention concerns a process for preparing 3-(3-chloro-1H-pyrazol-1-yl)pyridine (5b),

(5b)

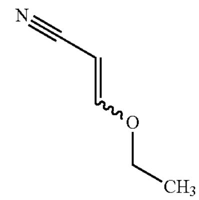


which comprises

a) treating 3-hydrazinopyridine.dihydrochloride

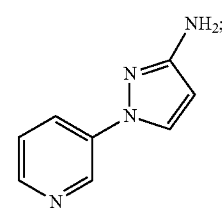


with 3-ethoxyacrylonitrile



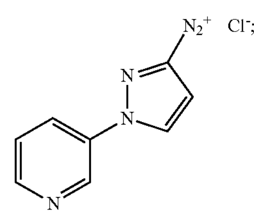
in a (C_1-C_4) aliphatic alcohol at a temperature of about 25° C. to about 100° C. in the presence of an alkali metal (C_1-C_4) alkoxide to provide 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a)

(8a)



b) treating the 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a) in aqueous hydrochloric acid with sodium nitrite at a temperature of about 0° C. to about 25° C. to provide the diazonium salt (8b)

(8b)



and

c) treating the diazonium salt (8b) with copper chloride at a temperature of about 0° C. to about 25° C.

DETAILED DESCRIPTION

The present invention provides an improved process for preparing 3-(3-chloro-1H-pyrazol-1-yl)pyridine (5b) by cyclizing 3-hydrazinopyridine.dihydrochloride with commercially available 3-ethoxyacrylonitrile to provide 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a), and by converting the amino group to a chloro group by a Sandmeyer reaction.

In the first step, 3-hydrazinopyridine.dihydrochloride is treated with 3-ethoxyacrylonitrile in a (C_1-C_4) aliphatic alcohol at a temperature of about 25° C. to about 100° C. in the presence of an alkali metal (C_1-C_4) alkoxide to provide 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a). While stoichiometric amounts of 3-hydrazinopyridine.dihydrochloride and 3-ethoxyacrylonitrile are required, it is often convenient to use about a 1.5 fold to about a 2 fold excess of 3-ethoxyacrylonitrile. The cyclization is run in the presence of an alkali metal (C_1-C_4) alkoxide base. It is often convenient to use about a 2 to about a 5 fold excess of base. The cyclization is performed in a (C_1-C_4) aliphatic alcohol. It is most convenient that the alkoxide base and the alcohol solvent be the same, for example, sodium ethoxide in ethanol. It is appreciated that methoxyacrylonitrile and propoxyacrylonitrile would be suitable for effecting this cyclization.

In a typical reaction, 3-hydrazinopyridine.dihydrochloride and an anhydrous alcohol are introduced into a reaction vessel and the alkoxide base is gradually added. The mixture is stirred and the 3-ethoxyacrylonitrile is added. The mixture is stirred at about 80° C. until most of the 3-hydrazinopyridine has reacted. The mixture is allowed to cool and the excess base is neutralized with acid. The crude 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a) is conveniently isolated and purified by standard techniques.

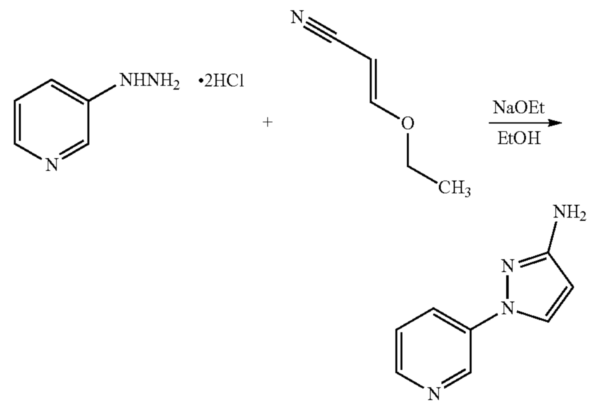
The 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a) is then converted to the desired 3-(3-chloro-1H-pyrazol-1-yl)pyridine (5b) by treatment in aqueous hydrochloric acid with sodium nitrite at a temperature of about 0° C. to about 25° C. to provide a diazonium salt followed by treatment of the diazonium salt with copper chloride at a temperature of about 0° C. to about 25° C. While stoichiometric amounts of reagents are required, it is often convenient to use an excess of reagents with respect to the 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a). Thus, aqueous hydrochloric acid is used in large excess as the reaction medium. Sodium nitrite is used in about a 1.3 fold to about a 2 fold excess. Copper chloride is used in about 5 mole percent to about 60 mole percent excess, preferably from about 15 mole percent to about 30 mole percent excess. The copper chloride may be either copper(I) chloride or copper(II) chloride. To suppress foaming during the reaction a water-immiscible organic solvent such as toluene or chloroform can be added during the treatment of the diazonium salt with copper chloride.

In a typical reaction, a mixture of 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a) and aqueous hydrochloric acid are mixed and cooled to about 0° C. An aqueous solution of sodium nitrite is slowly added maintaining the temperature below about 5° C. The suspension is stirred at about 0° C. for about 2 hours. In a separate vessel, a mixture of copper(I) chloride and toluene is cooled to about 0° C. and the chilled suspension of diazonium salt is added at a rate maintaining the temperature below about 5° C. The mixture is allowed to warm to about ambient temperature. After completion of the reaction, the mixture is treated with aqueous sodium hydroxide to adjust the pH to about 8 to about 10. The resulting solution is extracted with a water-immiscible organic solvent. After removal of the solvent, the 3-(3-chloro-1H-pyrazol-1-yl)pyridine (5b) can be used directly in the next step or further purified by standard techniques such as flash column chromatography or crystallization.

The following examples are presented to illustrate the invention.

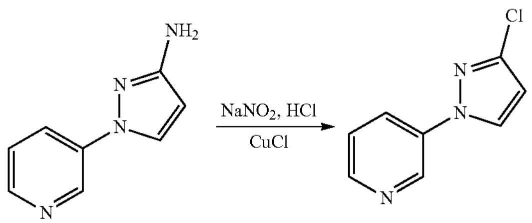
Examples

1. Preparation of 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a)



To a three-neck round bottomed flask (50 mL) equipped with a reflux condenser was introduced 3-hydrazinopyridine.dihydrochloride (1.82 g, 10.0 mmol) and anhydrous ethanol (10.0 mL). Sodium ethoxide (21 wt % in EtOH, 11.8 mL, 31.5 mmol) was added over 5 minutes and the internal temperature increased from 23° C. to 30° C. The resultant light brown slurry turned light pink after stirring for 10 minutes. 3-Ethoxyacrylonitrile (2.06 mL, 20.0 mmol) was added over 5 minutes and the internal temperature remained at 30° C. The yellow mixture was stirred at 78° C. under nitrogen for 5 hours and was then cooled to 15° C. Hydrochloric acid (4 M in 1,4-dioxane, 2.90 mL) was added slowly to quench any excess base forming a light brown suspension. The mixture was concentrated under reduced pressure to afford a brown solid. The solid was partitioned in water (30 mL) and ethyl acetate (50 mL). The insoluble light brown solid was collected by filtration to afford the first portion of product (0.340 g, >95% pure by ^{1}H NMR). The aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic extracts were concentrated to afford dark brown wet solid. The mixture was suspended in ethyl acetate (10 mL), filtered, and washed with heptane (20 mL) to afford the second portion of product as a brown solid (1.00 g, >95% pure by ^{1}H NMR). The title compound was obtained as a brown solid (1.34 g, 84%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J=2.4 Hz, 1H), 8.33 (dd, J=4.8, 1.2 Hz, 1H), 8.23 (d, J=2.4 Hz, 1H), 8.01 (ddd, J=8.4, 2.8, 1.2 Hz, 1H), 7.42 (dd, J=8.4, 4.8 Hz, 1H), 5.80 (d, J=2.4 Hz, 1H), 5.19 (bs, 2H, —NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 144.7, 138.0, 136.2, 128.3, 123.9, 123.2, 97.1; EIMS m/z 160 ($[M]^+$); HPLC (Zorbax SB-C8 column, P/N: 863954-306; mobile phase: A=water (0.1% formic acid), B=acetonitrile (0.01% formic acid); Gradient from 5 to 100% acetonitrile over 15 minutes; flow: 1.0 mL/minute): t_R=1.95 minutes.

2. Preparation of 3-(3-chloro-1H-pyrazol-1-yl)pyridine (5b)

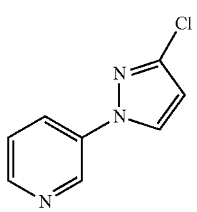


To a three-neck round bottomed flask (25 mL) was introduced 3-amino-1-(3-pyridyl)-pyrazole (0.480 g, 3.00 mmol) and concentrated hydrochloric acid (4.6 mL). The vigorously stirred mixture was cooled to −5° C. using a sodium chloride ice-bath. Sodium nitrite (0.269 g, 3.90 mmol) in water (1.3 mL) was added dropwise over 40 minutes while maintaining the temperature at −5° C. The resultant dark orange mixture was stirred for 1 hour between −5° C. and −0° C. and then added dropwise into a suspension of copper(I) chloride (0.475 g, 4.80 mmol) in chloroform (4.8 mL) at 25° C. over 15 minutes. The dark green slurry was stirred at room temperature for 1 hour. Water (10 mL) and chloroform (10 mL) was added to the mixture leading to a dark green solution. The acidic aqueous solution was neutralized by sodium hydroxide (50% in water) to pH 8 and extracted with chloroform (2×10 mL) and ethyl acetate (3×20 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product as a yellow solid (0.476 g). LC assay using di-n-propyl phthalate as internal standard indicated 73.7% purity (0.351 g, 65%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J=2.8 Hz, 1H), 8.57 (dd, J=4.8, 1.2 Hz, 1H), 8.03 (ddd, J=8.4, 2.8, 1.6 Hz, 1H), 7.90 (d, J=2.4 Hz, 1H), 7.41 (ddd, J=8.4, 4.8, 0.8 Hz, 1H), 6.45 (d, J=2.4 Hz, 1H); EIMS m/z 179 ($[M]^+$); HPLC (Zorbax SB-C8 column, P/N: 863954-306; mobile phase: A=water (0.1% formic acid), B=acetonitrile (0.01% formic acid); Gradient from 5 to 100% acetonitrile over 15 minutes; flow: 1.0 mL/minute): t_R=6.28 minutes.

What is claimed is:

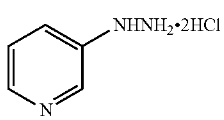
1. A process for preparing 3-(3-chloro-1H-pyrazol-1-yl) pyridine (5b),

(5b)



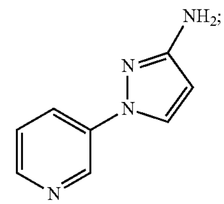
which comprises

a) treating 3-hydrazinopyridine.dihydrochloride



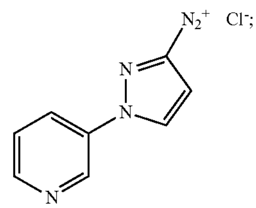
with between about a 1.5-fold to about a 2-fold excess of an alkoxyacrylonitrile in a (C_1-C_4) aliphatic alcohol at a temperature of about 25° C. to about 100° C. in the presence of an alkali metal (C_1-C_4) alkoxide to provide 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a)

(8a)



b) treating the 3-(3-amino-1H-pyrazol-1-yl)pyridine (8a) in aqueous hydrochloric acid with sodium nitrite in an excess of about 1.3-fold to about 2-fold at a temperature of about 0° C. to about 25° C. to provide the diazonium salt (8b)

(8b)



and

c) treating the diazonium salt (8b) with from about 5 mole percent to about 60 mole percent excess of a copper chloride a temperature of about 0° C. to about 25° C.

2. The process of claim **1** in which a water immiscible organic solvent is added in step c) to suppress foaming.

3. The process of claim **1**, wherein the alkoxyacrylonitrile is methoxyacrylonitrile, ethoxyacrylonitrile or propoxyacrylonitrile.

4. The process of claim **3**, wherein the alkoxyacrylonitrile is methoxyacrylonitrile.

5. The process of claim **3**, wherein the alkoxyacrylonitrile is ethoxyacrylonitrile.

6. The process of claim **3**, wherein the alkoxyacrylonitrile is propoxyacrylonitrile.

7. The process of claim **1**, wherein the alkali metal (C_1-C_4) alkoxide is sodium ethoxide, and the (C_1-C_4) aliphatic alcohol is ethanol.

8. The process of claim **1**, wherein the copper chloride is in about 15 mole percent to about 30 mole percent excess.

9. The process of claim **1**, wherein the copper chloride is copper (I) chloride.

10. The process of claim **1**, wherein the copper chloride is copper (II) chloride.

11. The process of claim **2**, wherein the water immiscible organic solvent is toluene or chloroform.

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